

Please add the following new claim:

--14. A method of treating hyperlipidemia in a hyperlipidemic comprising dosing the hyperlipidemic with an effective antihyperlipidemic amount of a compound metabolized to nicotinic acid by the body and selected from the group consisting of nicotinyl alcohol tartrate, d-glucitol hexanicotinate, aluminum nicotinate, and, 1-alpha-tocopheryl nicotinate, once per day in the evening or at night combined with at least one pharmaceutically acceptable carrier. --

REMARKS

Applicant proposes to add claim 14 by amendment. Claims 1-9, 13 and 14 will be pending in the present application after the present amendment is entered. Applicant proposes to amend the claims to more clearly define what the applicant considers to be the invention. Support for the language "oral solid dosage form" in claim 1 can be found at least on page 3, last paragraph, of the specification. Support for the language "250 milligrams to about 3000 milligrams of nicotinic acid" in claim 2 can be found at least on page 4, last paragraph, of the specification. Support for new claim 14 can be found at least on page 4 (second paragraph) and original claim 1. Applicant respectfully requests that the present amendments be entered after final rejection, as they place the application in better condition for allowance. For the examiner's convenience, applicant attaches a copy of the proposed, revised claims as Exhibit A. No new matter has been added by way of these amendments.

Applicant thanks the examiner for the courteous and helpful interview conducted in her office on March 22, 1995, regarding proposed claim amendments and a proposed Rule 131 declaration.

In the office action dated November 27, 1995, the examiner made two rejections. In response, applicant respectfully submits the following remarks.

I. Rejection Under 35 USC §112, Second Paragraph

The examiner has rejected claims 4-6, 8 and 9 under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. In particular, the examiner has stated that the claims lack antecedent basis for the language "or compound metabolized to nicotinic acid by the body." Applicant proposes to amend the claims to delete the phrase "or compound metabolized to nicotinic acid by the body." Thus, this basis for rejection now is moot.

In light of the amendments and remarks above, applicant requests the examiner to withdraw the rejection to the claims under 35 USC §112, second paragraph. Reconsideration of the claims is respectfully requested.

II. Rejection Under 35 USC §102(e)

The examiner has rejected claims 1-9 under 35 USC §102(e), as being unpatentable in view of O'Neill et al., U.S. patent No. 5,268,181 (1993). Applicant respectfully submits that the present Rule 131 declaration overcomes this basis for rejection.

The examiner has cited the O'Neill patent for the description of a method for treating hyperlipidemia by administration of a single dose of niacin at night. The applicant notes that the O'Neill patent was filed as a continuation-in-part application on June 29, 1992, and that the parent application of Evenstad et al. does not describe

administration of a single dose of niacin at night.¹ Accordingly, the relevant date for consideration under §102(e) is June 29, 1992.²

In the previous response, applicant filed a Rule 131 declaration to antedate the O'Neill patent. The examiner, however, has stated that the declaration was inadequate to antedate the reference because, *inter alia*, the declaration did not establish a reduction to practice of the presently claimed invention in the United States prior to June 29, 1992. Applicant respectfully submits that the present Rule 131 declaration is sufficient to antedate the O'Neill patent. See the Declaration Under 37 CFR §1.131, which is attached to this response as Exhibit B.

In particular, the declaration explains that, in 1990, KOS Pharmaceuticals, Inc., the assignee of the above-captioned application, sponsored a study to compare the effect on serum lipids of sustained release nicotinic acid that was administered once-a-day (either in the evening or at night) or twice-a-day during the day ("the KOS Pharmaceuticals study"). *Id.* at paragraph 4. The study was conducted with patients that were considered to have high cholesterol levels, and they were classified as hyperlipidemics. *Id.* Accordingly, the study was performed to determine a method of treating hyperlipidemia in hyperlipidemics comprising the administration of an effective amount of nicotinic acid once per day in the evening or at night.

The results of the KOS Pharmaceuticals study, disclosed in the above-captioned application and in the parent application,

¹ For the examiner's convenience, applicant submits herewith applicant's copies of the file histories of the O'Neill patent and its two parent applications, U.S. serial Nos. 536,184 and 337,460.

² As discussed in the response filed on August 23, 1995, the presently claimed invention of the above-captioned application is fully supported by the disclosure of the parent application, U.S. serial No. 08/124,392, filed on September 20, 1993.

demonstrated that treatment with nicotinic acid (once per day at night) was associated with a highly statistically significant decrease in blood cholesterol levels in hyperlipidemics. See the Rule 131 declaration at paragraph 5. Thus, the administration of a sustained release formulation of nicotinic acid (once per day in the evening or at night) was shown to be an effective treatment for hyperlipidemia.

A question arose during the interview at the PTO about whether the results of the KOS Pharmaceuticals study, presented in Exhibit 3 of the Rule 131 declaration, demonstrate a "method of treating hyperlipidemia in a hyperlipidemic." This issue was based upon the observation that, while treatment decreased total blood cholesterol levels in the subjects, certain subjects still had total blood cholesterol levels in the hyperlipidemic range after treatment.

First, applicant respectfully notes that the claims are directed to a method of treating hyperlipidemia, and not a method for curing hyperlipidemia. The data presented in the Rule 131 declaration fully supports a method for treating hyperlipidemia since the data show that the method decreases total blood cholesterol levels.

Moreover, applicant respectfully emphasizes that any decrease in total cholesterol levels is therapeutically useful. This point is highlighted by the results of a Lipid Research Clinics Program study which indicated that an 8% decrease in total blood cholesterol levels was associated with a 19% lower incidence of coronary heart disease. See Exhibit C.

The Rule 131 declaration also states that the KOS Pharmaceuticals study, including data analysis, was performed in the United States. See the Rule 131 declaration at paragraph 6. Moreover, although the last visit for the last patient took place on March 20, 1991, statistical analyses were performed each time data was entered into the database. *Id.* Consequently, a statistically significant reduction in total cholesterol was observed at least by December 31, 1990. *Id.*

In sum, the KOS Pharmaceuticals study verified a method of treating hyperlipidemia in a hyperlipidemic comprising the administration of nicotinic acid once per day in the evening or at night. Furthermore, nicotinic acid was administered to patients in combination with a pharmaceutically acceptable carrier. Accordingly, "a method of treating hyperlipidemia in a hyperlipidemic comprising dosing the hyperlipidemic with an effective antihyperlipidemic amount of nicotinic acid once per day in the evening or at night combined with at least one pharmaceutically acceptable carrier" was conceived and reduced to practice in the United States prior to June 29, 1992, the filing date of the O'Neill patent.

Applicant respectfully notes that:

The 37 CFR 1.131 affidavit or declaration must establish possession of either the whole invention claimed or something falling within the claim (such as a species of a claimed genus) in the sense that the claim as a whole reads on it.

Manual of Patent Examining Procedure §715.02 (Rev. 1, September 1995). Applicant respectfully asserts, therefore, that the presently submitted Rule 131 declaration fully supports the method of claim 1 recited in the above paragraph.

To expedite prosecution, however, applicant proposes to amend claim 1 to focus the claimed invention on a method that requires administration of nicotinic acid in an "oral solid dosage form." Applicant also proposes to delete the term "formulation" in dependent claims 6 and 8 for the sake of consistency.

Finally, in regard to the previous Rule 131 declaration, the examiner has stated that "[t]here is no record of PVP + niacin + lubricating agents." Office action of November 27, 1995, at page 3. However, applicant notes that in the KOS Pharmaceuticals study, patients received nicotinic acid in the form of sustained release tablets containing nicotinic acid, hydroxypropylmethylcellulose, Povidone and stearic acid, as shown in Table I of both the above-captioned application and the parent

application. Povidone is also known as "polyvinylpyrrolidone," as stated in monograph 7700 in THE MERCK INDEX, 11th Edition (Merck & Co. 1989) at page 1219. See Exhibit 5 of the Rule 131 declaration of David J. Bova. Moreover, stearic acid is a lubricating agent. See, for example, page 5, fourth full paragraph, of the parent Bova application. Accordingly, the use of a formulation for treating hyperlipidemia that comprises nicotinic acid, hydroxypropylmethylcellulose, polyvinylpyrrolidone and the lubricant, stearic acid, also antedates the filing date of the O'Neill patent.

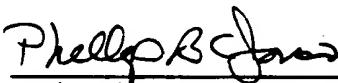
In light of the amendments, declaration and remarks above, applicant requests the examiner to withdraw the rejection to the claims under 35 USC §102(e). Reconsideration of the claims is respectfully requested.

CONCLUSION

Applicant requests reconsideration of the claims on their merits and respectfully solicit early notification of an allowance. If Examiner Venkat should have any questions or believes a telephone discussion would expedite prosecution, the examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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Date


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